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APPLICATION NO.	FILING DATE	FIRST NAMED INVENTOR	ATTORNEY DOCKET NO.	CONFIRMATION NO.
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JAMES F HALEY JR
FISH & NEAVE
1251 AVENUE OF THE AMERICAS
NEW YORK, NY 100201104

EXAMINER	
SOUAYA, JEHANNE E	

ART UNIT	PAPER NUMBER
1634	

DATE MAILED: 10/20/2003

Please find below and/or attached an Office communication concerning this application or proceeding.

Office Action Summary	Application No.	Applicant(s)	
	08/484,786	MACH ET AL.	
	Examiner	Art Unit	
	Jehanne E Souaya	1634	

-- *The MAILING DATE of this communication appears on the cover sheet with the correspondence address* --

Period for Reply

A SHORTENED STATUTORY PERIOD FOR REPLY IS SET TO EXPIRE 3 MONTH(S) FROM THE MAILING DATE OF THIS COMMUNICATION.

- Extensions of time may be available under the provisions of 37 CFR 1.136(a). In no event, however, may a reply be timely filed after SIX (6) MONTHS from the mailing date of this communication.
- If the period for reply specified above is less than thirty (30) days, a reply within the statutory minimum of thirty (30) days will be considered timely.
- If NO period for reply is specified above, the maximum statutory period will apply and will expire SIX (6) MONTHS from the mailing date of this communication.
- Failure to reply within the set or extended period for reply will, by statute, cause the application to become ABANDONED (35 U.S.C. § 133).
- Any reply received by the Office later than three months after the mailing date of this communication, even if timely filed, may reduce any earned patent term adjustment. See 37 CFR 1.704(b).

Status

1)☒ Responsive to communication(s) filed on *17 June 2003* .

2a)☒ This action is **FINAL**. 2b)☐ This action is non-final.

3)☐ Since this application is in condition for allowance except for formal matters, prosecution as to the merits is closed in accordance with the practice under *Ex parte Quayle*, 1935 C.D. 11, 453 O.G. 213.

Disposition of Claims

4)☒ Claim(s) *76-102* is/are pending in the application.

4a) Of the above claim(s) _____ is/are withdrawn from consideration.

5)☐ Claim(s) _____ is/are allowed.

6)☒ Claim(s) *76-102* is/are rejected.

7)☐ Claim(s) _____ is/are objected to.

8)☐ Claim(s) _____ are subject to restriction and/or election requirement.

Application Papers

9)☐ The specification is objected to by the Examiner.

10)☐ The drawing(s) filed on _____ is/are: a)☐ accepted or b)☐ objected to by the Examiner.

Applicant may not request that any objection to the drawing(s) be held in abeyance. See 37 CFR 1.85(a).

11)☐ The proposed drawing correction filed on _____ is: a)☐ approved b)☐ disapproved by the Examiner.

If approved, corrected drawings are required in reply to this Office action.

12)☐ The oath or declaration is objected to by the Examiner.

Priority under 35 U.S.C. §§ 119 and 120

13)☐ Acknowledgment is made of a claim for foreign priority under 35 U.S.C. § 119(a)-(d) or (f).

a)☐ All b)☐ Some * c)☐ None of:

1.☐ Certified copies of the priority documents have been received.

2.☐ Certified copies of the priority documents have been received in Application No. _____ .

3.☐ Copies of the certified copies of the priority documents have been received in this National Stage application from the International Bureau (PCT Rule 17.2(a)).

* See the attached detailed Office action for a list of the certified copies not received.

14)☐ Acknowledgment is made of a claim for domestic priority under 35 U.S.C. § 119(e) (to a provisional application).

a) ☐ The translation of the foreign language provisional application has been received.

15)☐ Acknowledgment is made of a claim for domestic priority under 35 U.S.C. §§ 120 and/or 121.

Attachment(s)

1) ☐ Notice of References Cited (PTO-892)
2) ☐ Notice of Draftsperson's Patent Drawing Review (PTO-948)
3) ☐ Information Disclosure Statement(s) (PTO-1449) Paper No(s) _____ .
4) ☐ Interview Summary (PTO-413) Paper No(s). _____ .
5) ☐ Notice of Informal Patent Application (PTO-152)
6) ☐ Other: .

DETAILED ACTION

1. Currently, claims 76-102 are pending in the instant application. All the amendments and arguments, as well as the declaration filed under 37 C.F.R. 1.132 have been thoroughly reviewed but are deemed insufficient to place this application in condition for allowance. The following rejections are reiterated. They constitute the complete set being presently applied to the instant Application. Response to Applicant's arguments follow. This action is FINAL.

2. The text of those sections of Title 35, U.S. Code not included in this action can be found in a prior Office action.

Response to 37 C.F.R. § 1.132 Declaration

3. The response contained a Declaration by Jack L. Strominger, M.D., D.Sc., under 37 C.F.R. 1.132. This declaration as well as previous declarations have been thoroughly reviewed but were found unpersuasive in overcoming the rejections under 35 USC 112/first paragraph (lack of enablement, lack of written description) for the following reasons.

At section 5 of the declaration, Dr. Strominger disagrees with the examiner's assertion that "the claims, as written, encompass polynucleotides and methods of using polynucleotides that vary substantially in length and in nucleotide composition". At section 6 of the declaration, Dr. Strominger asserts that statements made in paragraphs 15 and 16 of Dr. Strominger's previous declaration (May 16, 2002) were intended to demonstrate that "with the three polymorphic HLA-DR-β sequences and one conserved HLA-DR-β sequence, in hand, a person skilled in the art of HLA-DR-β typing would have understood that the designated

'polymorphism' of the three disclosed HLA-DR-β DNA sequences provided the 'common structural feature' by which the nucleotide sequences of additional polymorphic regions, namely 8-14, 26-32, and 72-78 of the HLA-DRB1 locus could be obtained." This was not found persuasive for the following reasons. Firstly, the claims encompass methods of using sequences and kits containing sequences which need only encode any of these 3 regions. In addition, these claims do not refer to any specific sequence of such regions. Therefore, the sequences in the claims do in fact encompass sequences that vary in length and nucleotide composition. While the specification teaches that these regions are polymorphic, the specification does not teach what polymorphisms could be tolerated in these regions and still be considered an HLA-DR-β-A allele, for example. Without such guidance, the skilled artisan would unable to predictably correlate, as of the time of filing of the instant invention, what these alleles would look like. Additionally, while the sequences disclosed in the specification could be used to find additional alleles, this is not a description of the alleles themselves. The specification teaches how to *find* additional sequences, this is not the same thing as teaching what these sequences *are* or what they would be predictably expected to look like. Exhibit K of applicants' response of March 3, 2002 provided an alignment of DRB alleles up to 2002. A number of variations, which are not described in the specification, occur within the 3 "polymorphic" regions in alleles found after the effective filing date of the instant invention. In addition, variations were found in the regions termed "constant" by the specification. These changes were not taught, nor did the specification provide any guidance as to the scope of changes within ~~these~~ the polymorphic regions that could be tolerated.

In section 7 of the declaration, Dr. Strominger asserts that the polymorphic nature of the nucleotide sequence located at positions 8-14, 26-32 and 72-78 of the HLA-DR-β allele would provide useful structural information for the identification of other HLA-DR alleles. This was not found persuasive. As stated above, although the specification teaches that these regions are polymorphic, the specification does not teach the scope of polymorphisms which could be tolerated in these regions and still be considered an HLA-DR-β allele, for example. Without such guidance, the skilled artisan would be unable to predictably correlate, as of the time of filing of the instant invention, what these alleles would look like. Additionally, while the sequences disclosed in the specification could be used to find additional alleles, the fact that they may be isolated using the sequences disclosed in the specification does not set forth a description of the DNA itself.

In section 8, Dr. Strominger asserts that the examiner's statement "the specification has not taught which positions within these regions can be changed and still be HLA-DR beta alleles and be used in a typing method" is not an accurate interpretation of the invention. This is not found persuasive. Firstly, as stated above, the claims as written encompass methods of typing involving sequences as well as kits comprising sequences that vary substantially in length and nucleotide composition. The examiner's statements were made with regard to the full scope of the *claimed* (emphasis added) invention. Previous responses and declarations continue to assert that the disclosed 3 polymorphic regions and single constant region would be useful in identifying further HLA-DR alleles. The examiner does not disagree with this statement. However, as of the effective filing date of the instant invention, the disclosure in the specification that 3 regions are polymorphic, and only one example of these polymorphisms as

well as a single "constant" sequence, is not representative of the large number of sequences encompassed by the claims. The disclosure in the specification is neither a description of what the large number of possible alleles are, nor does it provide a predictable correlation as to the identity of alleles that would still be HLA-DR beta alleles and still be useful for typing. Dr. Strominger's assertion in section 11, is an illustration of this point. In section 11, Dr. Strominger asserts "that the examiner is correct that the conserved sequence provided would not be useful in obtaining a cDNA from which the HLA-DRB4 allele sequences could be established." Dr. Strominger states that this is irrelevant in practice "because typing is never carried out for the HLA-DRB3, HLA-DRB4, and HLA-DRB5 alleles because these alleles are encoded at loci distinct from the DRB1 locus and the genes expressed at these loci are minor HLA sequences of no importance in typing." However, such sequences are encompassed by both the methods of typing and kits of the instant invention. Dr. Strominger's statements reflect further unpredictable experimentation that was required, *in addition* to the disclosure in the specification, to determine that "typing is never carried out for the HLA-DRB3, HLA-DRB4, and HLA-DRB5 alleles because these alleles are encoded at loci distinct from the DRB1 locus and the genes expressed at these loci are minor HLA sequences of no importance in typing". The disclosure in the specification provides no guidance or predictability as to such findings.

In section 9 of the declaration, Dr. Strominger asserts "a person of skill in the art, as of July 30, 1982 would recognize that 'any' nucleotide change within the polymorphic regions that did not result in a gross change in the structure of the HLA-DR-β chain would be tolerated, and thus useful in a HLA typing method." This was not found persuasive because the specification did not teach, at the time of filing, that "'any' nucleotide change within the polymorphic regions

that did not result in a gross change in the structure of the HLA-DR-β chain" would be considered an HLA-DR-β allele and "be useful for typing". Further, there is no disclosure or guidance in the specification, that sequences such as DRB4 sequences (identified after the specification was filed) would not be useful for typing. Dr. Strominger further asserts that some variations shown in exhibit K of the March 2002 response are a "very minor" fraction of the entire population and would not diminish the importance and usefulness of the conserved region. Firstly, the examiner has not questioned the importance or usefulness of the alleles disclosed in the specification. However, 35 USC 112/first paragraph provides that the specification must enable the full scope of the claimed invention. As outlined above, and discussed in the rejections below, the disclosure of the specification does not enable one of skill in the art to make or use the full scope of the claimed invention without undue experimentation.

Sections 10-12 of Dr. Strominger's declaration have been addressed above.

Maintained Rejections

Double Patenting

4. Claims 76-102 stand rejected under the judicially created doctrine of obviousness -type double patenting as being unpatentable over claims 1-10 of US Patent No. 5,503,976. This rejection is maintained pending the filing of a terminal disclaimer.

Claim Rejections - 35 USC § 112

Written Description

5. Claims 76-79 and 82-102 are rejected under 35 U.S.C. 112, first paragraph, as containing subject matter which was not described in the specification in such a way as to reasonably convey to one skilled in the relevant art that the inventor(s), at the time the application was filed, had possession of the claimed invention.

Claims 76-77 are broadly drawn to an HLA-DR typing method by hybridizing a DNA sample with a sequence that can hybridize to a polymorphic region of an HLA-DR beta chain locus wherein the sequence encodes amino acids 8-14, 26-32, and 72-78. Claims 78-79, and 84-85 are broadly drawn to an HLA-DR typing method in which sample DNA is hybridized to a DNA sequence encoding "a majority" of the region defined by amino acids 8-14, 26-32, 39-45, or 72-78 of a polypeptide encoded by DR-beta-A, DR-beta-B, or DR-beta-C. Claims 82-83 are drawn to methods of HLA DR typing by hybridizing a DNA sample with a sequence that can hybridize to constant region of an HLA-DR-beta chain locus wherein the sequence encodes amino acids 39-45. Claims 86, and 87-93 are dependent upon these claims. Claims 94-102 are drawn to kits containing a sequence that can hybridize to a polymorphic region of an HLA-DR-beta chain locus wherein the polymorphic region encodes amino acids 8-14, 26-32, and 72-78 or a sequence which can hybridize to a conserved region of an HLA-DR-beta locus at amino acids 39-45.

The specification has described polynucleotides consisting of DR-beta-A, -B, and -C and described the regions with the polypeptide encoded by these polynucleotides, i.e. amino acids 8-14, 24-32 and 72-78 which are variable between -A, -B, and -C and a region which is conserved

between -A, -B, and -C, that is amino acids 39-45 and describes methods of using these polynucleotides for HLA-DR typing. However, the claims, as written, encompass polynucleotides and methods of using polynucleotides that vary substantially in length and in nucleotide composition, including polynucleotides containing genomic DNA that have not been taught or described in the specification. Since the specification has only described three specific DR-beta sequences and because the genus of sequences encompassed by the recitation in the claims is large with no common structural feature other than amino acids 38-45 (it is noted that amino acids 8-14, 24-32, and 72-78 are variable between -A, -B, and -C), the three species described in the specification are not representative of the broadly claimed genus. Furthermore, the prior art does not provide compensatory structural or correlative teachings that would enable the skilled artisan to identify or predict the nucleotide composition of the large number of sequences encompassed for use in the methods.

The claims encompass typing methods in which the DNA minimally encoding all or part of amino acids 8-14, 26-32 or 72-78 of any HLA-DR-beta chain is used to determine one or more HLA alleles. However, the specification has only described three specific DR-beta chain coding sequences. Because of the polymorphic nature of these genes, there may be many different DR-beta chain sequences of which three is not representative. Furthermore, the claims, as written encompass using genomic sequences as well as the cDNA sequences, but the genomic DNA sequence has not been described in the specification to establish that applicant was in possession of genomic sequences at the time of filing. Additionally, the claims are drawn to methods using DNA sequences which are capable of hybridizing to polymorphic sequences which makes the genus of DNA sequences which can be used in the method even larger. The

large genus of sequences identified by the broad scope of "hybridization" (ie: large range of hybridization conditions) would not all predictably have the same structural characteristics as the disclosed species because there is no way to determine what variations would be tolerated without trial and error analysis to determine what variations could be made without making the method inoperable as a typing method. Further, the specification provides no teaching or description as to which positions within the regions taught in the specification, including the conserved region, can be altered or varied such that the regions are still characteristic of HLA-DR-β alleles. The specification has not set forth a functional correlation between the different structures encompassed by the method such that a predictable correlation can be made with regard to which variations can and cannot be used for typing.

Although the specification teaches that amino acids 38-45 are conserved, and teaches the polymorphic sequences of amino acids 8-14, 26-32, and 72-78 for the -A, -B, and -C alleles, the claims are not limited to such sequences but instead to undisclosed sequences whose nucleotide composition can vary in these regions as well as other regions of HLA-DR-beta, including genomic DNA sequences (all claims encompass DNA sequences which include such genomic sequences, or methods of using such DNA sequences), which have not been taught or described in the specification. Such recitations in the claims include: sequences encoding a "majority of the amino acids in the region" (claims 78-79, and claims which depend therefrom), "sequences capable of hybridizing to" (claims 76-79, 82-93, 95-98 and 100-102), " a region consisting essentially of amino acids 39-45" (claims 84-85, 101, and sequences which depend therefrom). Claims 78-79 are not supported by the description in the specification because the claims encompass a typing method using a DNA sequence which minimally, encodes "a majority" of a

region of amino acids 8-14, 26-32, 39-45 or 72-78 of HLA-DR-beta -A, -B, -C, or allelic variants. The DNA sequences used in the claim methods include a very large genus of sequences including genomic sequences, coding sequences for DR-beta chains, different from those described in the specification as well as sequences which do not encode the same "conserved" region taught in the specification as a result of the language used such as "sequences capable of hybridizing to" and " a region consisting essentially of amino acids 39-45". The claims are not limited to the DNA sequences consisting of the specifically described regions of amino acids 8-14, 26-32, 39-45 and 72-78 of DR-beta, -A, -B, and -C of this application, but instead encompass large DNA sequences which encode only a few amino acids from these regions. The DNA sequence is not even limited to coding for the same amino acids as in the described regions because the claims recite that DNA encodes a majority of the region defined by amino acids or "is capable of hybridizing to" these regions, which allows for considerable nucleotide and amino acid variation from the sequences disclosed in the specification. The three polymorphic sequences described do not constitute a representative number of species of the claimed genus of nucleic acids which include variants in the described regions, sequences that hybridize to the sequences disclosed, sequences from other species, and genomic sequences. None of these sequences meet the written description provision of 35 USC 112, first paragraph. The specification has not taught which sequences within these regions can be changed and still be useful in a typing method. While the sequence of each nucleic acid in the claimed genus need not be disclosed to fulfill the written description requirement, to establish that applicants were in possession of such changes the specification should describe what changes are encompassed by the full scope of the claims and provide a correlation between the

structure of the alterations encompassed by the claims and whether they would be considered HLA-DR-beta alleles and be used for typing . University of California v. Eli Lilly and Co., 43 USPQ2d 1398, 1404, 1405 held that:

To fulfill the written description requirement, a patent specification must describe an invention and do so in sufficient detail that one skilled in the art can clearly conclude that "the inventor invented the claimed invention." Lockwood v. American Airlines, Inc., 107 F.3d 1565, 1572, 41 USPQ2d 1961, 1966 (1997); In re Gosteli, 872 F.2d 1008, 1012, 10 USPQ2d 1614, 1618 (Fed. Cir. 1989) (" [T]he description must clearly allow persons of ordinary skill in the art to recognize that [the inventor] invented what is claimed."). Thus, an applicant complies with the written description requirement "by describing the invention, with all its claimed limitations, not that which makes it obvious," and by using "such descriptive means as words, structures, figures, diagrams, formulas, etc., that set forth the claimed invention." Lockwood, 107 F.3d at 1572, 41 USPQ2d at 1966.

An adequate written description of a DNA, such as the cDNA of the recombinant plasmids and microorganisms of the '525 patent, "requires a precise definition, such as by structure, formula, chemical name, or physical properties," not a mere wish or plan for obtaining the claimed chemical invention. Fiers v. Revel, 984 F.2d 1164, 1171, 25 USPQ2d 1601, 1606 (Fed. Cir. 1993). Accordingly, "an adequate written description of a DNA requires more than a mere statement that it is part of the invention and reference to a potential method for isolating it; what is required is a description of the DNA itself." Id. at 1170, 25 USPQ2d at 1606.

The response and declaration filed 3/22/2002 provide an alignment of HLA-DR-beta sequences known up to 2002. From this alignment, it is clear that amino acids in each of the 4 regions taught in the specification can be varied, however the specification has not taught or described a predictable correlation between which positions can be varied in such regions and be considered HLA-DR-beta alleles and still be used for typing. Vas-Cath Inc. v. Mahurkar, 19 USPQ2d 1111, makes clear that "applicant must convey with reasonable clarity to those skilled in the art that, as of the filing date sought, he or she was in possession of the invention. The invention is, for purposes of the 'written description' inquiry, whatever is now claimed." (See page 1117.) The specification does not "clearly allow persons of ordinary skill in the art to recognize that [he or she] invented what is claimed." (See Vas-Cath at page 1116.) With the exception of sequences disclosed in the specification, the skilled artisan cannot envision the detailed chemical structure of the encompassed polynucleotides and/or proteins, regardless of the

complexity or simplicity of the method of isolation. Adequate written description requires more than a mere statement that it is part of the invention and reference to a potential method for isolating it. The nucleic acid itself is required. See Fiers v. Revel, 25 USPQ2d 1601, 1606 (CAFC 1993), and Amgen Inc. V. Chugai Pharmaceutical Co. Ltd., 18 USPQ2d 1016. In Fiddes v. Baird, 30 USPQ2d 1481, 1483, claims directed to mammalian FGF's were found unpatentable due to lack of written description for the broad class. The specification provided only the bovine sequence.

Accordingly, the specification lacks adequate written description for the methods and kits of claims 76-79 and 82-102.

Response to Arguments

6. The response traverses the rejection. The response asserts that the Written Description Guidelines emphasize that "describing the complete chemical structure, ie, the DNA sequence, of a claimed DNA" is only one method of describing the DNA. Other methods include "relevant identifying characteristics to provide evidence that the applicants were in possession of the claimed invention, ie, complete or partial structure, functional characteristics when coupled with a known or disclosed function or structure, or some combination." The response asserts that the Examiner's contentions are without merit, particularly when viewed in light of the Declaration by Dr. Strominger, at section 6. This argument was thoroughly reviewed but was not found persuasive. Firstly, the claims encompass methods of using sequences and kits containing sequences which need only encode any of ~~these 3~~ the 4 regions. In addition, these claims do not refer to any specific sequence of such regions. Therefore, the sequences in the claims do in fact encompass sequences that vary in length and nucleotide composition. While the specification

teaches that these regions are polymorphic, the specification does not teach what polymorphisms could be tolerated in these regions and still be considered an HLA-DR-β allele. Without such guidance, the skilled artisan would unable to determine, as of filing of the instant invention, what these alleles would look like. Although, the sequences disclosed in the specification could be used to find additional alleles, this is not a description of the alleles themselves. The specification discloses sequences which could be used to *find* additional sequences, this is not the same thing as teaching what these sequences *are* or what they would be expected to look like. Exhibit K of applicants' response of March 3, 2002 provided an alignment of DRB alleles up to 2002. A number of variations, which are not described in the specification, occur within the 3 "polymorphic" regions in alleles found after the effective filing date of the instant invention. In addition, variations were found in the regions termed "constant" by the specification. As such, it is clear that these changes were not taught or described in the specification.

The response further asserts that the findings in The Regents of the University of California v. Eli Lilly Company does not apply to the sequence of the instant claims because these sequences are from the same species and Dr. Strominger provides expert testimony which states that the DNA sequences taught by applicants provides enough structural detail to identify additional HLA-DR-β alleles. These arguments have been thoroughly reviewed but were found unpersuasive. Firstly, as in Lilly, the instant claims encompass sequences from different species (for example, claim 95 is drawn to a kit comprising a sequence which hybridizes to an HLA-DR-β chain locus of human lymphocyte antigen...". Sequences from other species, however, can and would be expected to hybridize to human sequences). Secondly, Dr. Strominger's testimony provides for finding additional sequences, this is not a description of the DNA itself. Adequate

written description requires more than a mere statement that it is part of the invention and reference to a potential method for isolating it. The nucleic acid itself is required. See Fiers v. Revel, 25 USPQ2d 1601, 1606 (CAFC 1993), and Amgen Inc. V. Chugai Pharmaceutical Co. Ltd., 18 USPQ2d 1016. For these reasons, and the reasons made of record in previous office actions, the rejection is maintained.

Enablement

7. Claims 76-79 and 82-102 are rejected under 35 U.S.C. 112, first paragraph, as containing subject matter which was not described in the specification in such a way as to enable one skilled in the art to which it pertains, or with which it is most nearly connected, to make and/or use the invention.

There are many factors to be considered when determining whether there is sufficient evidence to support determination that a disclosure does not satisfy the enablement requirements and whether any necessary experimentation is undue (See In re Wands, 858 F. 2d 731, 8 USPQ2d 1400, 1404 (Fed. Cir. 1988)). These factors include, but are not limited to:

Quantity of Experimentation Necessary
Amount of Direction and Guidance
Presence and Absence of Working Examples
Nature of the Invention
Level of predictability and unpredictability in the art

Claims 76-77 are broadly drawn to an HLA-DR typing method by hybridizing a DNA sample with a sequence that can hybridize to a polymorphic region of an HLA-DR beta chain locus wherein the sequence encodes amino acids 8-14, 26-32, and 72-78. Claims 78-79 and 84-85 are broadly drawn to an HLA-DR typing method in which sample DNA is hybridized to a

DNA sequence encoding "a majority" of the region defined by amino acids 8-14, 26-32, 39-45, or 72-78 of a polypeptide encoded by DR-beta-A, DR-beta-B, or DR-beta-C. Claims 82-83 are drawn to methods of HLA DR typing by hybridizing a DNA sample with a sequence that can hybridize to constant region of an HLA-DR-beta chain locus wherein the sequence encodes amino acids 39-45. Claims 86, and 87-93 are depending upon these claims. Claims 94-102 are drawn to kits containing a sequence that can hybridize to a polymorphic region of an HLA-DR-beta chain locus wherein the polymorphic region encodes amino acids 8-14, 26-32, and 72-78 or a sequence which can hybridize to a conserved region of an HLA-DR-beta locus at amino acids 39-45.

The specification has described polynucleotides consisting of DR-beta-A, -B, and -C and described the regions with the polypeptide encoded by these polynucleotides, i.e. amino acids 8-14, 24-32 and 72-78 which are variable between -A, -B, and -C and a region which is conserved between -A, -B, and -C, that is amino acids 39-45 and describes methods of using these polynucleotides for HLA-DR typing. However, the claims, as written, encompass polynucleotides and methods of using polynucleotides that vary substantially in length and in nucleotide composition. Since the specification has only described three specific DR-beta sequences and because the genus of sequences encompassed by the broad scope of the claims is enormous with no common structural feature other than amino acids 38-45 (it is noted that amino acids 8-14, 24-32, and 72-78 are variable between -A, -B, and -C), the three sequences described in the specification do not enable the skilled artisan to make or use the broad scope of the claimed invention without undue experimentation. Furthermore, the prior art does not provide compensatory structural or correlative teachings to enable the skilled artisan to identify or predict

the nucleotide composition of the large number of sequences encompassed for use in the methods.

The claims encompass typing methods in which the DNA minimally encodes amino acids 8-14, 26-32 or 72-78 of any HLA-DR-beta chain is used to determine one or more HLA alleles. However, the specification has only described three specific DR-beta chain coding sequences. Because of the polymorphic nature of these genes, there may be many different DR-beta chain sequences, which the specification does not teach. Additionally, the claims are drawn to methods using DNA sequences which are capable of hybridizing to polymorphic sequences which makes the genus of DNA sequences which can be used in the method even larger. The large genus of sequences identified by the broad scope of "hybridization" (ie: large range of hybridization conditions) would not all predictably have the same structural characteristics as the disclosed sequences because there is no way to determine what variations would be tolerated without trial and error analysis to determine what variations could be made, for example, within the "conserved region, such that the nucleic acids would still be HLA-DR-beta alleles and useful for typing HLA-DR-beta. Although hybridization methods were known and used in the art at the time of filing, such hybridization methods, to identify the variants encompassed by the broadly claimed invention, are unpredictable with regard to what variations encompassed by the broadly claimed invention would be useful for typing HLA-DR-beta. Further, the specification has not set forth a functional correlation between the different variations within the disclosed structures encompassed by the method such that a predictable correlation can be made with regard to which variations can and cannot be used for typing, or which variations could be made and still be encompassed by the broadly claimed nucleic acid sequences.

Although the specification teaches that amino acids 39-45 are conserved, and teaches the polymorphic sequences of amino acids 8-14, 26-32, and 72-78 for the -A, -B, and -C alleles, the claims are not limited to such sequences but instead to undisclosed sequences whose nucleotide composition can vary in these regions as well as other regions of HLA-DR-beta, including genomic DNA sequences (all claims encompass DNA sequences which include such genomic sequences, or methods of using such DNA sequences), which have not been taught or described in the specification. Such recitations in the claims include: sequences encoding a "majority of the amino acids in the region" (claims 78-79, and claims which depend therefrom), "sequences capable of hybridizing to" (claims 76-79, 82-93, 95-98 and 100-102), " a region consisting essentially of amino acids 39-45" (claims 84-85, 101, and sequences which depend therefrom). Claims 78-79 are not supported by the description in the specification because the claims encompass a typing method using a DNA sequence which minimally, encodes "a majority" of a region of amino acids 8-14, 26-32, 39-45 or 72-78 of HLA-DR-beta -A, -B, -C, or allelic variants. The DNA sequences used in the claimed methods include a very large genus of sequences including genomic sequences, coding sequences for DR-beta chains, different from those described in the sequence as well as sequences which do not encode DR-beta changes as a result of the language used such as "sequences capable of hybridizing to" and " a region consisting essentially of amino acids 39-45" . The claims are not limited to the DNA sequences consisting of the specifically described regions of amino acids 8-14, 26-32, 39-45 and 72-78 of DR-beta, -A, -B, and -C of this application, but instead encompass large DNA sequences which only encode only a few amino acids from these regions. The DNA sequence is not even limited to coding for the same amino acids as in the described regions because the claims recite that

DNA encodes a majority of the region defined by amino acids or "is capable of hybridizing to" these regions, which allows for considerable nucleotide and amino acid variation from the sequences disclosed in the specification. The specification has not taught which positions within these regions can be changed and still be HLA-DR beta alleles and useful in a typing method. The response and declaration provide an alignment of HLA-DR-beta sequences known up to 2002. From this alignment, it is clear that amino acids in each of the 4 regions taught in the specification can be varied, however the specification has not taught or described a predictable correlation between which positions can be varied within such regions, including the "conserved" region and still be used for typing or which positions can be varied within the disclosed regions and still be identified as DR-beta alleles. As the art does not provide any correlative teachings to make up for the deficiencies in the specification, the skilled artisan would be required to perform trial and error analysis to establish a predictable correlation between the variations in nucleic acids used in the broadly claimed methods and encompassed by the broadly claimed kits and the identity of HLA-DR-beta alleles which can tolerate such variations.

Response to Arguments

8. The response traverses the rejection. The response asserts that Dr. Strominger believes that as of July 30, 1982, it would have been possible for one of skill in the art to use the conserved and polymorphic DNA sequences disclosed in the '786 application to identify other HLA-DR-β alleles. This argument was not found persuasive. Firstly, although one of skill in the art could use the sequences disclosed in the '786 application to identify other alleles, this does not make up for the fact that the identity of these alleles is unpredictable. For instance, the specification terms the region of amino acids 39-45 as "constant", however, additional DRB4

alleles have been subsequently found to be variable in this region (see exhibit K of the response filed March 2002). Dr. Strominger's testimony characterizes a method for finding other sequences. The specification, however, has not established predictably, what sequences are encompassed by DR-beta alleles. Secondly, the Court in Genetech Inc. V Novo Nordisk 42 USPQ2d 1001 held that "(I)t is the specification, not the knowledge of one skilled in the art that must supply the novel aspects of the invention in order to constitute adequate enablement". In addition, the method claims are not drawn to using all four regions (the 3 polymorphic regions and single constant region), but to using any of these regions singly.

With regard to the response's assertions concerning the remainder of Dr. Strominger's 2nd declaration, such are reiterated. With regard to section 9 of the declaration: the specification did not teach, at the time of filing, that "'any' nucleotide change within the polymorphic regions that did not result in a gross change in the structure of the HLA-DR-β chain" would be considered an HLA-DR-β allele and "be useful for typing". Further, there is no disclosure or guidance in the specification, that sequences such as DRB4 sequences (identified after the specification was filed) would not be useful for typing. Dr. Strominger further asserts that some variations shown in exhibit K of the March 2002 response are a "very minor" fraction of the entire population and would not diminish the importance and usefulness of the conserved region. Firstly, the examiner has not questioned the importance or usefulness of the alleles disclosed in the specification. However, 35 USC 112/first paragraph provides that the specification must enable the full scope of the claimed invention. As outlined above, the disclosure of the specification does not enable one of skill in the art to make or use the full scope of the claimed invention without undue experimentation.

With regard to the response's traversal of the examiners statement that "the specification has not taught the variations within the DRB4 alleles which were later identified such that the skilled artisan would have known at the time of filing that such variations would still be DR-beta alleles." The disclosure in the specification is neither a description of what the large number of possible alleles are, nor does it provide a predictable correlation as to the identity of alleles that would still be HLA-DR beta alleles and still be useful for typing. Dr. Strominger's assertion in section 11, is an illustration of this point. In section 11, Dr. Strominger asserts "that the examiner is correct that the conserved sequence provided would not be useful in obtaining a cDNA from which the HLA-DRB4 allele sequences could be established." Dr. Strominger states that this is irrelevant in practice, however, "because typing is never carried out for the HLA-DRB3, HLA-DRB4, and HLA-DRB5 alleles because these alleles are encoded at loci distinct from the DRB1 locus and the genes expressed at these loci are minor HLA sequences of no importance in typing." However, such sequences are encompassed by both the methods of typing and kits of the instant invention. The DRB3 and DRB5 alleles shown in exhibit K are polymorphic in regions of amino acids 8-14, 26-32, and 72-78, and constant in region of amino acid 39-45, however, as stated by Dr. Strominger, these sequences are not used for typing. Dr. Strominger's statements reflect further unpredictable, experimentation that was required, *in addition* to the disclosure in the specification, to determine that "typing is never carried out for the HLA-DRB3, HLA-DRB4, and HLA-DRB5 alleles because these alleles are encoded at loci distinct from the DRB1 locus and the genes expressed at these loci are minor HLA sequences of no importance in typing". The disclosure in the specification provides no guidance or predictability as to such findings.

The arguments made in the response and declaration continue to refer to specific sequences that have been disclosed in the specification as well as all 4 regions (the 3 polymorphic as well as the single constant region), however the scope of the claims are much broader. The claims only generally refer to DNA encoding amino acid regions, not to specific sequences themselves. Further, the methods of typing are not limited to using the 4 regions outlined in the specification. As such, the scope of the claims do not bear a reasonable correlation to the scope of enablement provided by the specification. Case law has established that "(t)o be enabling, the specification of a patent must teach those skilled in the art how to make and use the full scope of the claimed invention without 'undue experimentation.'" In re Wright 990 F.2d 1557, 1561. In re Fisher, F.2d 833, 839, 166 USPQ 18, 24 (CCPA 1970) it was determined that "(t)he scope of the claims must bear a reasonable correlation to the scope of enablement provided by the specification to persons of ordinary skill in the art". For these reasons and the reasons made of record in the previous office action, the rejection is maintained.

Conclusion

9. Applicant's amendment necessitated the new ground(s) of rejection presented in this Office action. Accordingly, **THIS ACTION IS MADE FINAL**. See MPEP § 706.07(a). Applicant is reminded of the extension of time policy as set forth in 37 CFR 1.136(a).

A shortened statutory period for reply to this final action is set to expire THREE MONTHS from the mailing date of this action. In the event a first reply is filed within TWO MONTHS of the mailing date of this final action and the advisory action is not mailed until after the end of the THREE-MONTH shortened statutory period, then the shortened statutory period

will expire on the date the advisory action is mailed, and any extension fee pursuant to 37 CFR 1.136(a) will be calculated from the mailing date of the advisory action. In no event, however, will the statutory period for reply expire later than SIX MONTHS from the date of this final action.

10. No claims are allowable.

11. Any inquiry concerning this communication or earlier communications from the examiner should be directed to examiner Jehanne Souaya whose telephone number is (703) 308-6565. The examiner can normally be reached Monday-Friday from 9:00 AM to 6:00 PM.

If attempts to reach the examiner by telephone are unsuccessful, the examiner's supervisor, Gary Jones, can be reached on (703) 308-1152. The fax phone number for this Group is (703) 872-9306.

Any inquiry of a general nature should be directed to the Group receptionist whose telephone number is (703) 308-0196.

Jehanne Souaya

Jehanne Souaya
Primary Examiner
Art Unit 1634
10/16/2003